

ORIGINAL ARTICLE

Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes

Satish K. Garg, M.D., Robert R. Henry, M.D., Phillip Banks, M.S., John B. Buse, M.D., Ph.D., Melanie J. Davies, M.D., Gregory R. Fulcher, M.D., Paolo Pozzilli, M.D., Diane Gesty-Palmer, M.D., Ph.D., Pablo Lapuerta, M.D., Rafael Simó, M.D., Ph.D., Thomas Danne, M.D., Darren K. McGuire, M.D., M.H.Sc., Jake A. Kushner, M.D., Anne Peters, M.D., and Paul Strumph, M.D.

ABSTRACT

BACKGROUND

In most patients with type 1 diabetes, adequate glycemic control is not achieved with insulin therapy alone. We evaluated the safety and efficacy of sotagliflozin, an oral inhibitor of sodium–glucose cotransporters 1 and 2, in combination with insulin treatment in patients with type 1 diabetes.

METHODS

In this phase 3, double-blind trial, which was conducted at 133 centers worldwide, we randomly assigned 1402 patients with type 1 diabetes who were receiving treatment with any insulin therapy (pump or injections) to receive sotagliflozin (400 mg per day) or placebo for 24 weeks. The primary end point was a glycated hemoglobin level lower than 7.0% at week 24, with no episodes of severe hypoglycemia or diabetic ketoacidosis after randomization. Secondary end points included the change from baseline in glycated hemoglobin level, weight, systolic blood pressure, and mean daily bolus dose of insulin.

RESULTS

A significantly larger proportion of patients in the sotagliflozin group than in the placebo group achieved the primary end point (200 of 699 patients [28.6%] vs. 107 of 703 [15.2%], $P<0.001$). The least-squares mean change from baseline was significantly greater in the sotagliflozin group than in the placebo group for glycated hemoglobin (difference, -0.46 percentage points), weight (-2.98 kg), systolic blood pressure (-3.5 mm Hg), and mean daily bolus dose of insulin (-2.8 units per day) ($P\leq 0.002$ for all comparisons). The rate of severe hypoglycemia was similar in the sotagliflozin group and the placebo group (3.0% [21 patients] and 2.4% [17], respectively). The rate of documented hypoglycemia with a blood glucose level of 55 mg per deciliter (3.1 mmol per liter) or below was significantly lower in the sotagliflozin group than in the placebo group. The rate of diabetic ketoacidosis was higher in the sotagliflozin group than in the placebo group (3.0% [21 patients] and 0.6% [4], respectively).

CONCLUSIONS

Among patients with type 1 diabetes who were receiving insulin, the proportion of patients who achieved a glycated hemoglobin level lower than 7.0% with no severe hypoglycemia or diabetic ketoacidosis was larger in the group that received sotagliflozin than in the placebo group. However, the rate of diabetic ketoacidosis was higher in the sotagliflozin group. (Funded by Lexicon Pharmaceuticals; inTandem3 ClinicalTrials.gov number, NCT02531035.)

From the University of Colorado Denver, Aurora (S.K.G.); the University of California at San Diego, San Diego (R.R.H.); Lexicon Pharmaceuticals, The Woodlands (P.B., D.G.-P., P.L., P.S.), the University of Texas Southwestern Medical Center, Dallas (D.K.M.), and Baylor College of Medicine and Texas Children's Hospital, Houston (J.A.K.) — all in Texas; the Diabetes Research Center, University of North Carolina School of Medicine, Durham (J.B.B.); the University of Leicester and University Hospitals of Leicester NHS Trust, Leicester, United Kingdom (M.J.D.); the University of Sydney, Sydney (G.R.F.); University Campus Bio-Medico of Rome, Rome (P.P.); Vall d'Hebron Research Institute, Barcelona, and CIBERDEM-Instituto de Salud Carlos III, Madrid (R.S.); Diabetes Center Auf der Bult, Hannover Medical School, Hannover, Germany (T.D.); and the University of Southern California, Los Angeles (A.P.). Address reprint requests to Dr. Satish Garg at the Barbara Davis Center for Diabetes, University of Colorado Denver, 1775 Aurora Court, Rm. M20-1323, Aurora, CO 80045, or at satish.garg@ucdenver.edu.

A complete list of the inTandem3 primary investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 13, 2017, at NEJM.org.

DOI: [10.1056/NEJMoa1708337](https://doi.org/10.1056/NEJMoa1708337)

Copyright © 2017 Massachusetts Medical Society.

THE INCIDENCE OF TYPE 1 DIABETES, which currently affects 29 million adults worldwide, is rising.¹ In the United States, the number of patients with type 1 diabetes who are younger than 20 years of age may triple within 30 years.² Less than one third of adults with type 1 diabetes achieve a glycated hemoglobin level lower than 7.0%, and most are overweight or obese.³⁻⁵ Patients with type 1 diabetes also face risks of complications or death from severe hypoglycemia and diabetic ketoacidosis.⁶⁻¹⁰ The ideal treatment for type 1 diabetes should enable patients to maintain a glycated hemoglobin level lower than 7.0% without weight gain or an increased risk of hypoglycemia and diabetic ketoacidosis.

Sotagliflozin (LX4211) is a new oral inhibitor of sodium–glucose cotransporters 1 and 2 (SGLT1 and SGLT2). SGLT1 inhibition reduces glucose absorption in the proximal intestine, which significantly blunts and delays postprandial hyperglycemia. SGLT2 inhibition decreases renal glucose reabsorption.¹¹⁻¹³ In phase 2 studies, the administration of sotagliflozin improved glycemic control and lowered body weight among patients with type 1 or 2 diabetes; it also reduced glycemia, despite a decreased bolus dose of insulin, among patients with type 1 diabetes.^{14,15} No oral medication has been approved for use in combination with insulin to lower the glucose level in patients with type 1 diabetes. We report the results of the inTandem3 trial, a phase 3 clinical trial that assessed the effects of sotagliflozin as compared with placebo with respect to glycemic control and the occurrence of severe hypoglycemia and diabetic ketoacidosis among adults with type 1 diabetes who were receiving their usual insulin therapy.

METHODS

TRIAL DESIGN AND OVERSIGHT

This multicenter, randomized, double-blind, placebo-controlled trial, which was conducted at 133 sites in 19 countries, evaluated the safety and efficacy of sotagliflozin in combination with insulin therapy (pump or injections) in patients with type 1 diabetes. After a 2-week, single-blind run-in period during which all patients received placebo, eligible patients were randomly assigned, in a 1:1 ratio, to receive either sotagliflozin (400 mg per day) or placebo for 24 weeks.

Efficacy and safety were assessed at prespecified times during the treatment period, and a final safety assessment was performed 30 days after the last dose of the trial regimen was administered.

The institutional review board at each trial center approved the protocol (available with the full text of this article at NEJM.org) and the consent form. All patients provided written informed consent before participation. An independent clinical end-point committee, whose members were unaware of the treatment assignments, adjudicated events of special interest, including severe hypoglycemia, diabetic ketoacidosis, major adverse cardiovascular events, drug-induced liver injury, and death. An independent data and safety monitoring committee reviewed adverse events. An independent statistician performed the statistical analysis. The trial was sponsored by Lexicon Pharmaceuticals and was conducted as a collaboration between the sponsor and an academic steering committee. A clinical research organization (Covance) executed the trial. The first and last authors wrote the first draft of the manuscript with medical-writing assistance (funded by Lexicon Pharmaceuticals). All the authors had full access to the trial data and participated in preparing the manuscript for submission (for further details, see the Supplementary Appendix, available at NEJM.org). The first author made the decision to submit the manuscript for publication and vouches for the completeness and accuracy of the data and analysis and the fidelity of the trial to the protocol.

PATIENTS

Men and nonpregnant women 18 years of age or older who had had type 1 diabetes for at least 1 year were eligible for participation in the trial if they met the following inclusion criteria: treatment with insulin at a stable basal dose for at least 2 weeks before the screening visit, a glycated hemoglobin level of 7.0 to 11.0%, and a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of at least 18.5. All the patients were required to perform self-monitoring of blood glucose levels. Key exclusion criteria were severe hypoglycemia or diabetic ketoacidosis during the previous month, two or more episodes of diabetic ketoacidosis during the previous 6 months, and an estimated glomerular filtration rate lower than 45 ml per minute per 1.73 m² of body-surface area. (For a

complete list of enrollment criteria, see the Supplementary Appendix.)

PROCEDURES

In the sotagliflozin group, patients received the 400-mg dose of sotagliflozin as two 200-mg oral tablets, which they took once daily before the first meal of the day. In the placebo group, patients took two matching placebo tablets in the same manner. The patients continued their existing regimens with any approved insulin, except on the day that they received the first dose of the trial regimen, when they received a 30% lower dose of mealtime insulin for the first meal.¹⁴ Investigators subsequently adjusted insulin doses to meet target blood glucose levels during self-monitoring (fasting or preprandial target level, 80 to 130 mg per deciliter [4.4 to 7.2 mmol per liter]; 2-hour or peak postprandial target level, <180 mg per deciliter [10.0 mmol per liter]). (For further details about insulin-dose algorithms, see the Supplementary Appendix.) Investigators could individualize target levels, and use of devices for personal continuous glucose monitoring was allowed. Results of laboratory tests for glycated hemoglobin and fasting plasma and urinary glucose levels were masked to trial staff after randomization. From week 16 until the end of the trial, investigators were informed about glycated hemoglobin levels higher than 11.0% so that necessary changes could be implemented. Investigators maintained patients' baseline antihypertensive medications until week 16, unless patient safety was compromised.

All the trial participants received information about the detection and treatment of ketosis and about urogenital hygiene, proper hydration, the use of urinary ketone strips, and the use of β -hydroxybutyrate meters and strips. Trial centers received recommendations for the diagnosis and management of ketosis and diabetic ketoacidosis (for further details, see the Supplementary Appendix).

END POINTS

The primary end point was a glycated hemoglobin level lower than 7.0% at week 24, with no episodes of severe hypoglycemia or diabetic ketoacidosis after randomization. Prespecified secondary end points were the change from baseline to week 24 in glycated hemoglobin level, body weight, and mean daily bolus dose of insulin

(based on the doses administered during the 3 to 5 days before the trial visit, including correction doses) and the change from baseline to week 16 in systolic blood pressure among patients who had a systolic blood pressure of 130 mm Hg or higher at baseline.

Other prespecified end points were defined according to various combinations of the following criteria: a threshold for glycated hemoglobin level (i.e., a level <7.0% or a $\geq 0.5\%$ reduction in the level from baseline), a threshold for body weight, and no episode of severe hypoglycemia or diabetic ketoacidosis. Single end points included the change from baseline to week 16 in diastolic blood pressure and the change from baseline to week 24 in fasting plasma glucose level, urinary albumin-to-creatinine ratio, calcium-to-creatinine ratio, glucose-to-creatinine ratio, serum creatinine level, estimated glomerular filtration rate, and mean daily total and basal doses of insulin, as well as the number of documented hypoglycemic events (on the basis of blood glucose levels of ≤ 70 mg per deciliter [3.9 mmol per liter] and of ≤ 55 mg per deciliter [3.1 mmol per liter] during self-monitoring). The two thresholds for hypoglycemia were based on thresholds commonly used in previous trials for type 1 diabetes.

Severe hypoglycemia was defined as a hypoglycemic event that required assistance from another person or resulted in loss of consciousness or a seizure, regardless of the patient's glucose level. The diagnosis of diabetic ketoacidosis was based on the presence of anion-gap metabolic acidosis related to excessive ketone production without an alternative cause. (For detailed definitions, see the Supplementary Appendix.)

Safety information, including clinical and laboratory values and data on adverse events, was collected at each trial visit and during a final assessment, which was performed 30 days after the last dose of the trial regimen was administered. The rates of serious adverse events, adverse events of special interest, death, and discontinuation due to adverse events were recorded. Acidosis-related adverse events were prespecified.

STATISTICAL ANALYSIS

Efficacy and safety analyses were performed in the modified intention-to-treat population, which included all patients who underwent randomization and received at least one dose of the trial regimen. We assessed the superiority of sota-

gliflozin (400 mg per day) versus placebo with respect to the primary end point. We estimated that a sample size of 700 patients per trial group would give the trial at least 90% power to detect a target effect size in binomial proportions of approximately 0.10 for the primary end point, assuming that 50% of the participants overall would achieve the primary end point (i.e., an estimate that yielded a maximum sample size independent of the response rate among patients receiving placebo). This sample size would also allow a large enough safety population to reliably estimate between-group differences in rates of severe hypoglycemia. For the primary and secondary efficacy variables, the null hypothesis of no treatment effect was tested at a two-sided alpha level of 0.05. To control the overall type I error rate across these tests, a hierarchical procedure was applied. In a sensitivity analysis, the influence of missing data was assessed through the application of the imputation method for nonresponse for the primary end point and through the application of several multiple imputation methods for the secondary end points. Categorical variables were analyzed as proportions, and the results were summarized as a corresponding percentage point. Safety analyses were descriptive. (For further details about statistical methods, see the Supplementary Appendix.)

RESULTS

PATIENT CHARACTERISTICS

From October 2015 through September 2016, a total of 1405 patients underwent randomization; the trial was completed in April 2017. A total of 1402 patients (699 in the sotagliflozin group and 703 in the placebo group) received at least one dose of the trial regimen and were included in the modified intention-to-treat population. Baseline characteristics of the patients in each trial group are shown in Table 1. (For further details, see Fig. S1 and Table S1 in the Supplementary Appendix.)

PRESPECIFIED EFFICACY END POINTS

A significantly larger proportion of patients in the sotagliflozin group than in the placebo group achieved the primary end point of a glycated hemoglobin level lower than 7.0% at week 24 and no severe hypoglycemia or diabetic ketoacidosis (200 of 699 patients [28.6%] vs. 107 of 703

[15.2%]) (Fig. 1 and Table 2). The estimated between-group difference was 13.4 percentage points (95% confidence interval [CI], 9.0 to 17.8; $P<0.001$). Similarly, in the subgroup analysis according to type of insulin therapy (pump vs. no pump), approximately twice as many patients in the sotagliflozin group as in the placebo group, both among those who used an insulin pump and those who did not, achieved the primary end point. Among patients who had a glycated hemoglobin level of 7.0% or higher at week 24, the rate of diabetic ketoacidosis was significantly higher and the rate of severe hypoglycemia was nonsignificantly higher in the sotagliflozin group than in the placebo group (Table 2).

Significantly more patients in the sotagliflozin group than in the placebo group achieved a glycated hemoglobin level lower than 7.0% (207 patients [29.6%] vs. 111 [15.8%]). The reduction in the glycated hemoglobin level from baseline to week 24 was significantly greater in the sotagliflozin group than in the placebo group (difference, -0.46 percentage points; $P<0.001$), and greater reductions occurred among patients with higher baseline levels (including levels $\geq 7.7\%$, $>8.5\%$, and $>9.0\%$) (Fig. 1). (For further details, see Fig. S2 and Table S2 in the Supplementary Appendix.)

A significantly larger proportion of patients in the sotagliflozin group than in the placebo group achieved end points defined according to various combinations of the following criteria: a prespecified threshold for glycated hemoglobin level (i.e., a level $<7.0\%$ or a $\geq 0.5\%$ reduction in the level from baseline), a threshold for body weight (i.e., no weight gain or a $>5\%$ reduction in weight from baseline), and no episode of severe hypoglycemia or diabetic ketoacidosis. A glycated hemoglobin level lower than 7.0% was achieved with no weight gain in 171 patients (24.5%) in the sotagliflozin group and 51 patients (7.3%) in the placebo group. Among patients in either trial group who achieved a target glycated hemoglobin level, less than 2% had severe hypoglycemia and less than 2% had diabetic ketoacidosis; among those who had a 0.5% or greater reduction in the glycated hemoglobin level from baseline, the rate of diabetic ketoacidosis was significantly higher in the sotagliflozin group than in the placebo group. (For further details, see Fig. S3 and Table S3 in the Supplementary Appendix.)

The reduction in body weight from baseline

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Sotagliflozin (N = 699)	Placebo (N = 703)
Age — yr	43.3±14.2	42.4±14.0
Female sex — no. (%)	341 (48.8)	364 (51.8)
Race or ethnic group — no. (%)†		
White	619 (88.6)	621 (88.3)
Black	24 (3.4)	22 (3.1)
Asian	7 (1.0)	5 (0.7)
Hispanic	49 (7.0)	47 (6.7)
Native American or Alaska Native	1 (0.1)	5 (0.7)
Native Hawaiian or Other Pacific Islander	1 (0.1)	0
Other	47 (6.7)	50 (7.1)
Duration of diabetes — yr	20.5±12.4	19.6±12.1
Glycated hemoglobin — %	8.26±0.96	8.21±0.92
Fasting plasma glucose — mg/dl	165.1±71.6	163.4±69.1
Weight — kg	82.40±17.13	81.55±17.03
BMI‡	28.29±5.13	28.10±5.18
BMI ≥25 — no. (%)‡	495 (70.8)	497 (70.7)
Systolic blood pressure — mm Hg	122.0±15.3	121.8±14.8
Diastolic blood pressure — mm Hg	76.4±8.8	76.7±9.1
Systolic blood pressure ≥130 mm Hg — no. (%)	203 (29.0)	203 (28.9)
Daily total dose of insulin — IU/kg	0.69±0.28	0.71±0.29
Insulin dose — IU/day		
Total	56.88±27.60	58.35±29.09
Basal	29.54±16.29	29.63±15.54
Bolus and corrections	27.34±16.97	28.72±19.04
Type of insulin therapy — no. (%)§		
Subcutaneous injections	424 (60.7)	423 (60.2)
Pump	275 (39.3)	280 (39.8)

* Plus-minus values are means ±SD.

† Race or ethnic group was reported by the patient. Patients who reported Hispanic ethnic group could also report a race.

‡ Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

§ For further details about types of insulin therapy, see Table S1 in the Supplementary Appendix.

to week 24 was significantly greater in the sotagliflozin group than in the placebo group (difference, −2.98 kg; $P<0.001$). In the sotagliflozin group, the placebo-corrected reductions from baseline in the mean daily total, bolus, and basal doses of insulin were −5.3 units per day (−9.7%), −2.8 units per day (−12.3%), and −2.6 units per day (−9.9%), respectively ($P<0.001$ for all comparisons). Among patients with a systolic blood pressure of 130 mm Hg or higher at baseline, the reduction in systolic blood pressure from baseline to week 16 was significantly great-

er in the sotagliflozin group than in the placebo group (difference, −3.5 mm Hg; $P=0.002$). In addition, in the modified intention-to-treat population, the reductions in the fasting plasma glucose level and in systolic and diastolic blood pressure were significantly greater in the sotagliflozin group than in the placebo group, as were the increases in the calcium-to-creatinine ratio and glucose-to-creatinine ratio. However, the changes in the albumin-to-creatinine ratio, serum creatinine level, and estimated glomerular filtration rate did not differ significantly between

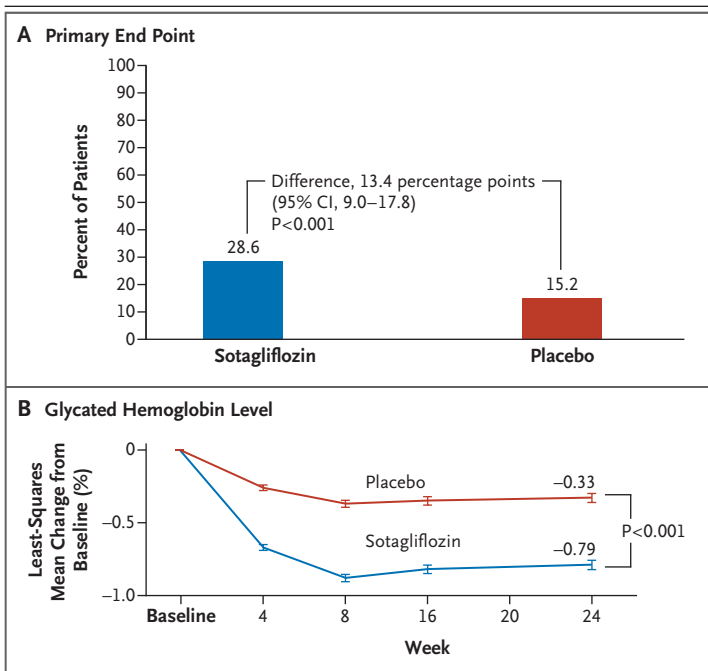


Figure 1. Primary and Secondary End Points.

Panel A shows the percentage of patients who achieved the primary end point of a glycated hemoglobin level lower than 7.0% at week 24, with no episodes of severe hypoglycemia or diabetic ketoacidosis after randomization. Panel B shows the least-squares mean change in the glycated hemoglobin level from baseline to week 24. The baseline level was 8.26% in the sotagliflozin group and 8.21% in the placebo group. I bars indicate standard errors. Analyses were performed in the modified intention-to-treat population, which included all patients who underwent randomization and received at least one dose of the trial regimen.

the trial groups. (For further details, see Figs. S4 and S5 and Tables S2 and S4 in the Supplementary Appendix.)

Results of sensitivity analyses, which were performed for the primary and secondary efficacy end points with the use of various imputation methods, confirmed the results of the main analyses.

DOCUMENTED HYPOGLYCEMIA

The percentage of patients who had an episode of documented hypoglycemia with a blood glucose level of 70 mg per deciliter or lower was similar in the sotagliflozin group and the placebo group (96.3% [673 of 699 patients] and 95.3% [670 of 703], respectively); the corresponding event rates were 69.8 per person-year and 77.9 per person-year. The event rate of documented hypoglycemia with a blood glucose level of 55 mg per deciliter or below was significantly lower in the sotagliflozin group than in the placebo group (11.8 per person-year and 15.4 per person-year, respectively) (Table 3, and Table S4 in the Supplementary Appendix).

SAFETY

The overall rate of adverse events (regardless of cause) was similar in the sotagliflozin group and the placebo group (55.1% [385 of 699 patients] and 52.5% [369 of 703], respectively) (Table 3). Most adverse events were mild to mod-

Table 2. Efficacy End Points.

End Point	Sotagliflozin (N=699)	Placebo (N=703)	Difference (95% CI)	P Value
	no./total no. (%)		percentage points	
Patients with glycated hemoglobin <7.0% and no severe hypoglycemia or diabetic ketoacidosis				
All patients	200/699 (28.6)	107/703 (15.2)	13.4 (9.0 to 17.8)	<0.001
Patients who used insulin pump	88/275 (32.0)	45/280 (16.1)	15.9 (8.6 to 23.3)	<0.001
Patients who did not use insulin pump	112/424 (26.4)	62/423 (14.7)	11.8 (6.1 to 17.4)	<0.001
Patients with glycated hemoglobin ≥7.0% and ≥1 episode of severe hypoglycemia*	16/699 (2.3)	13/703 (1.8)	0.4 (−1.0 to 1.9)	0.56
Patients with glycated hemoglobin ≥7.0% and ≥1 episode of diabetic ketoacidosis*	18/699 (2.6)	4/703 (0.6)	2.0 (0.7 to 3.3)	0.003

* These results are from a post hoc analysis that was performed with the use of asymptotic methods to summarize the differences in binomial proportions without stratification according to randomization factors. The small number of events suggested that stratified tests would not be sensible. This category included patients who had an event of interest and a glycated hemoglobin value of 7.0% or higher at week 24 or missing data at the 24-week assessment.

erate in severity. Gastrointestinal events (consistent with SGLT1 inhibition) and genital mycotic infections (consistent with SGLT2 inhibition) were more common in the sotagliflozin group than in the placebo group (Table 3, and Table S5 in the Supplementary Appendix). Diarrhea occurred in 29 patients (4.1%) in the sotagliflozin group and in 16 (2.3%) in the placebo group, and it led to discontinuation in 3 patients (0.4%) in the sotagliflozin group and none in the placebo group. Genital mycotic infection occurred in 45 patients (6.4%) in the sotagliflozin group and in 15 (2.1%) in the placebo group, and it led to discontinuation in less than 1% of patients in each trial group. Bone fractures occurred in 4 and 5 patients in the sotagliflozin and placebo groups, respectively. No amputations were reported during the trial.

More patients in the sotagliflozin group than in the placebo group had serious adverse events (48 patients [6.9%] vs. 23 [3.3%]), and more patients in the sotagliflozin group withdrew from the trial because of an adverse event (44 patients [6.3%] vs. 16 [2.3%]). One death (a suicide) occurred in the sotagliflozin group and was judged to be unrelated to the trial drug. Two major adverse cardiovascular events occurred in the sotagliflozin group.

One or more episodes of severe hypoglycemia occurred in 21 patients (3.0%) in the sotagliflozin group and in 17 (2.4%) in the placebo group. Among patients who used an insulin pump, one or more episodes of severe hypoglycemia occurred in more patients in the sotagliflozin group than in the placebo group (10 of 275 patients [3.6%] vs. 5 of 280 [1.8%]); the numbers among those who did not use an insulin pump were similar in the two groups (11 of 424 patients [2.6%] and 12 of 423 [2.8%], respectively). The trial regimen was discontinued due to severe hypoglycemia in 2 patients in the sotagliflozin group and in 1 in the placebo group.

The rate of acidosis-related adverse events at week 24 was 8.6% in the sotagliflozin group and 2.4% in the placebo group. The rate of one or more positively adjudicated episodes of diabetic ketoacidosis was higher in the sotagliflozin group than in the placebo group overall (3.0% vs. 0.6%), as well as among those who used an insulin pump (4.4% vs. 0.7%) and those who did not use an insulin pump (2.1% vs. 0.5%). The

trial regimen was discontinued due to an adjudicated diabetic ketoacidosis event in 11 patients (1.6%) in the sotagliflozin group and in 1 (0.1%) in the placebo group.

DISCUSSION

In the inTandem3 trial involving patients with type 1 diabetes who were receiving any approved insulin, the percentage of patients who achieved the primary end point of a glycated hemoglobin level lower than 7.0% at week 24 and no episode of severe hypoglycemia or diabetic ketoacidosis was higher in the group that received sotagliflozin than in the placebo group (28.6% vs. 15.2%). However, the rates of diabetic ketoacidosis and hypoglycemia were higher in the sotagliflozin group than in the placebo group. The use of sotagliflozin was also associated with significant decreases in glycated hemoglobin level, fasting plasma glucose level, insulin dose, weight, and systolic blood pressure.

Roughly two thirds of adult patients with type 1 diabetes have a glycated hemoglobin level of 7.0% or higher, and up to two thirds are overweight or obese.³⁻⁵ The baseline characteristics of the patients in our trial are consistent with these data; 71% of the patients had a baseline BMI of 25 or higher, and by design, all patients who underwent randomization had a glycated hemoglobin level of 7.0% or higher at screening. Reductions in the glycated hemoglobin level are usually associated with an increased incidence of hypoglycemia and weight gain.¹⁶ However, the target glycated hemoglobin level (<7.0%) was achieved in approximately twice as many patients in the sotagliflozin group as in the placebo group, and the target level was achieved without weight gain in three times as many patients in the sotagliflozin group as in the placebo group.

A composite end point of a glycated hemoglobin level lower than 7.0% and no hypoglycemia or weight gain is often used in studies of medications for the treatment of type 2 diabetes.¹⁷ The primary end point in our trial was established to assess for a net clinical benefit of achieving a target glycated hemoglobin level (<7.0%) in the absence of severe hypoglycemia and diabetic ketoacidosis. However, this end point did not assess for the absence or presence of severe hypoglycemia and diabetic ketoacidosis

Table 3. Summary of Adverse Events.*

Event	Sotagliflozin (N=699)	Placebo (N=703)
	no. of patients (%)	
Adverse events		
Any adverse event	385 (55.1)	369 (52.5)
Serious adverse event	48 (6.9)	23 (3.3)
Severe adverse event	16 (2.3)	9 (1.3)
Death	1 (0.1)†	0
Positively adjudicated adverse events		
Severe hypoglycemia, ≥1 episode‡	21 (3.0)	17 (2.4)
Severe nocturnal hypoglycemia, ≥1 episode‡	2 (0.3)	5 (0.7)
Severe hypoglycemia in a patient who used insulin pump, ≥1 episode§	10 (3.6)	5 (1.8)
Severe hypoglycemia in a patient who did not use insulin pump, ≥1 episode§	11 (2.6)	12 (2.8)
Diabetic ketoacidosis, ≥1 episode	21 (3.0)	4 (0.6)
Diabetic ketoacidosis in a patient who used insulin pump, ≥1 episode§	12 (4.4)	2 (0.7)
Diabetic ketoacidosis in a patient who did not use insulin pump, ≥1 episode§	9 (2.1)	2 (0.5)
Major adverse cardiovascular events	2 (0.3)	0
Myocardial infarction	1 (0.1)	0
Stroke	0	0
Hospitalization due to heart failure	0	0
Coronary revascularization	1 (0.1)	0
Liver injury	0	0
Investigator-reported events of special interest		
Volume depletion	13 (1.9)	2 (0.3)
Genital mycotic infection	45 (6.4)	15 (2.1)
Urinary tract infection	25 (3.6)	27 (3.8)
Diarrhea¶	29 (4.1)	16 (2.3)
Pancreatitis	0	0
Bone fracture	4 (0.6)	5 (0.7)
Potential drug-induced liver injury	2 (0.3)	0
Renal event	5 (0.7)	3 (0.4)
Cancer	1 (0.1)	2 (0.3)
Documented hypoglycemia‡	673 (96.3)	670 (95.3)
Documented nocturnal hypoglycemia‡	521 (74.5)	553 (78.7)
Blood glucose ≤55 mg/dl during self-monitoring	528 (75.5)	559 (79.5)
Hypoglycemic events		
Blood glucose ≤70 mg/dl during self-monitoring	69.8	77.9
Blood glucose ≤55 mg/dl during self-monitoring	11.8	15.4
Serious and nonserious acidosis-related adverse events	60 (8.6)	17 (2.4)
Serious acidosis-related adverse events	24 (3.4)	5 (0.7)
Nonserious acidosis-related adverse events	39 (5.6)	12 (1.7)
Positively adjudicated serious and nonserious acidosis-related adverse events	23 (3.3)	4 (0.6)
Positively adjudicated acidosis-related events that were also classified as diabetic ketoacidosis	21 (3.0)	4 (0.6)

Table 3. (Continued.)

Event	Sotagliflozin (N=699)	Placebo (N=703)
	no. of patients (%)	
Events that led to discontinuation		
Any adverse event that led to discontinuation	44 (6.3)	16 (2.3)
Any event of special interest that led to discontinuation**	21 (3.0)	5 (0.7)
Diarrhea	3 (0.4)	0
Genital mycotic infection	2 (0.3)	0
Urinary tract infection	0	2 (0.3)
Penile infection	1 (0.1)	0
Vulvovaginal candidiasis	1 (0.1)	0
Wrist fracture	1 (0.1)	0
Increase in hepatic enzyme	1 (0.1)	0
Severe hypoglycemia‡	2 (0.3)	1 (0.1)
Diabetic ketoacidosis	11 (1.6)	1 (0.1)
Acetonemia	1 (0.1)	0
Neoplasm	0	1 (0.1)
Renal failure	0	1 (0.1)

* Data are for patients who received at least one dose of the trial regimen and include events that occurred up to 30 days after the last dose of the trial regimen was administered. For the definitions of volume-depletion events, renal events, and acidosis-related events, see the Supplementary Appendix.

† The death was a suicide that was judged to be unrelated to the trial drug.

‡ Severe hypoglycemia was defined as a hypoglycemic event that required assistance from another person or resulted in loss of consciousness or a seizure, regardless of the patient's glucose level. Documented hypoglycemia was defined as a blood glucose level of 70 mg per deciliter or lower, with or without symptoms. Nocturnal hypoglycemia was defined as a hypoglycemic event that occurred between midnight and 5:59 a.m., regardless of whether the patient was awake during the event. Hypoglycemia was considered to be an event of special interest, with a specialized case-report form. Because the analysis for hypoglycemia was based on data recorded on this case-report form, investigators were asked not to report hypoglycemic events on the case-report form for adverse events unless the episode met criteria for a serious adverse event.

§ Percentages are based on the number of patients in the subgroup of patients who used a pump and the subgroup that did not use a pump, rather than on the total number of patients. In the sotagliflozin group, 275 patients used an insulin pump and 424 did not; in the placebo group, 280 patients used an insulin pump and 423 did not.

¶ Diarrhea was mostly transient and mild-to-moderate.

|| These data are reported as events per person-year.

** All events of special interest that led to discontinuation were investigator-reported, except for severe hypoglycemia and diabetic ketoacidosis, which were adjudicated.

among patients in the sotagliflozin group who did not achieve a glycated hemoglobin level lower than 7.0%.

In phase 2 trials, sotagliflozin, empagliflozin, and canagliflozin were associated with significant decreases in the glycated hemoglobin level among patients with type 1 diabetes.^{14,18,19} The design of our phase 3 trial allowed us to evaluate the effects of sotagliflozin in combination with insulin therapy in a setting that resembles day-to-day clinical practice. By week 24, the difference between the sotagliflozin group and the placebo group in the reduction of the glycated hemoglobin level from baseline was 0.46 percentage points. Slightly more patients in the sota-

gliflozin group than in the placebo group had severe hypoglycemia (21 and 17 patients, respectively), but the event rate (the rate per person-year) of documented hypoglycemia, with a threshold for blood glucose level of either ≤ 70 mg per deciliter or ≤ 55 mg per deciliter, was lower in the sotagliflozin group than in the placebo group. Modest but significant weight loss occurred in the sotagliflozin group, possibly because of increased glycosuria, reduced insulin doses, or other unknown factors. Sotagliflozin treatment also led to significant reductions in blood pressure.

Other randomized, controlled trials that have evaluated the adjunctive use of liraglutide, sita-

gliptin, and metformin in patients with type 1 diabetes have not shown consistent or sustained reductions in the glycated hemoglobin level or have shown increases in episodes of severe hypoglycemia or diabetic ketoacidosis.²⁰⁻²³ The use of off-label adjunctive therapy is uncommon, and the only therapy other than insulin that is approved for the treatment of type 1 diabetes is injectable pramlintide, which modestly reduces the glycated hemoglobin level and weight but is associated with an increased risk of severe hypoglycemia and is thus used infrequently.^{3,16,24} Reductions in the glycated hemoglobin level, systolic blood pressure, and weight must be maintained for a long-term period to reduce the risk of complications associated with diabetes, but mean changes in these outcomes may be less robust in short-term studies. Therefore, the decision to use adjunctive therapy can currently be based only on clinical assessment of metabolic needs in patients in whom insulin alone is unlikely to be sufficiently effective.

In our trial, the addition of sotagliflozin to existing insulin regimens improved glycemic control and led to reductions in the total, bolus, and basal doses of insulin. A decrease in insulin dose may be a risk factor for diabetic ketoacidosis.^{25,26}

Regulatory authorities have required that warnings about diabetic ketoacidosis be added to prescribing labels for the SGLT2 inhibitor class, because these agents have been associated with diabetic ketoacidosis in patients with type 1 or type 2 diabetes.^{19,26-34} When SGLT inhibitors are administered, monitoring for ketosis, particularly during metabolically stressful situations, is required.^{26,34} SGLT inhibitors should be discontinued before scheduled surgical procedures, and patients and clinicians should remain in close consultation regarding other forms of behavioral and physiological stress.^{26,35} Diabetic ketoacidosis may occur more frequently among those who use an insulin pump, because of kinked catheters, infusion-set problems, and other operational failures, and therefore, those who use an insulin pump may require closer monitoring.^{36,37} The basal insulin formulations used in subcutaneous-injection regimens, which have a longer duration of action than the rapid-acting insulin analogues used in pump regimens, may mitigate the risk of diabetic ketoacidosis.

Our trial has some limitations. First, the long-term effects of sotagliflozin cannot be determined from this 24-week trial. Second, data on

glycated hemoglobin levels were masked to investigators after screening to make the trial design consistent with other trials of sotagliflozin, and if investigators had had access to the data, they may have adjusted insulin therapy more aggressively to meet target glycated hemoglobin levels. Third, this trial employed measures to mitigate the risk of diabetic ketoacidosis that may have been more intensive than those used in typical clinical practice. Fourth, reductions in the glycated hemoglobin level, fasting plasma glucose level, and episodes of documented hypoglycemia suggest decreased glucose variability, but data from continuous glucose monitoring were not analyzed in this trial. Blinded data from continuous glucose monitoring will be analyzed in the recently completed inTandem1 and inTandem2 trials (ClinicalTrials.gov numbers, NCT02384941 and NCT02421510, respectively). Fifth, no artificial pancreas system had been approved at the time of trial initiation. Since sotagliflozin treatment was associated with a decrease in insulin dose, its use in patients who use a currently approved artificial pancreas system may require further evaluation.^{38,39}

In summary, among adult patients with type 1 diabetes who were receiving insulin therapy, the proportion of patients who achieved a glycated hemoglobin level lower than 7.0% and had no severe hypoglycemia or diabetic ketoacidosis was larger in the group that received sotagliflozin than in the placebo group. However, the rates of diabetic ketoacidosis and severe hypoglycemia were higher among patients who received sotagliflozin but did not achieve the target glycated hemoglobin level than among those who received placebo.

Supported by Lexicon Pharmaceuticals. (Lexicon Pharmaceuticals and Sanofi entered a license agreement, effective November 2015, and are collaborating on the development and commercialization of sotagliflozin.)

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the trial investigators, staff, and patients for their participation; Peng Zhang (Covance, Princeton, NJ) for performing independent statistical analysis; Amanda Justice and Kathryn Martin for providing medical-writing and editorial support (funded by Lexicon Pharmaceuticals) for an earlier version of the manuscript; and the following contributors for reviewing an earlier version of the manuscript: Timothy S. Bailey, M.D. (AMCR Institute, Escondido, CA), George Grunberger, M.D. (Grunberger Diabetes Institute, Bloomfield Hills, MI, and Wayne State University School of Medicine, Detroit), Sultan Linjawi, M.B., B.S. (Coffs Endocrine and Diabetes Services, Coffs Harbour, NSW, Australia), Rory J. McCrimmon, M.D., M.B., Ch.B. (University of Dundee, Dundee, United Kingdom), Catherine Petit, M.D. (Centre Hospitalier Sud Francilien, Corbeil-Essonnes, France), and Mark O'Neill, Dave R. Powell, M.D., and Sangeeta Sawhney, M.D. (Lexicon Pharmaceuticals, The Woodlands, TX).

REFERENCES

1. Diabetes atlas. 7th ed. Brussels: International Diabetes Federation, 2015.
2. Imperatore G, Boyle JP, Thompson TJ, et al. Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth. *Diabetes Care* 2012;35:2515-20.
3. Miller KM, Foster NC, Beck RW, et al. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry. *Diabetes Care* 2015;38:971-8.
4. McKnight JA, Wild SH, Lamb MJ, et al. Glycaemic control of Type 1 diabetes in clinical practice early in the 21st century: an international comparison. *Diabet Med* 2015;32:1036-50.
5. Weinstock RS, Schütz-Fuhrmann I, Connor CG, et al. Type 1 diabetes in older adults: comparing treatments and chronic complications in the United States T1D Exchange and the German/Austrian DPV registries. *Diabetes Res Clin Pract* 2016; 122:28-37.
6. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 2013;369:362-72.
7. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009; 32:1335-43.
8. Realsen J, Goettle H, Chase HP. Morbidity and mortality of diabetic ketoacidosis with and without insulin pump care. *Diabetes Technol Ther* 2012;14:1149-54.
9. National diabetes statistics report. Atlanta: Centers for Disease Control and Prevention, 2017 (<https://www.cdc.gov/diabetes/data/statistics/statistics-report.html>).
10. Number of emergency department visits (in thousands) with hypoglycemia as first-listed diagnosis and diabetes as secondary diagnosis, adults aged 18 years or older, United States, 2006–2009. Atlanta: Centers for Disease Control and Prevention, 2014 (<https://www.cdc.gov/diabetes/statistics/hypoglycemia/fig1.htm>).
11. Lapuerta P, Zambrowicz B, Strumph P, Sands A. Development of sotagliflozin, a dual sodium-dependent glucose transporter 1/2 inhibitor. *Diab Vasc Dis Res* 2015;12:101-10.
12. Zambrowicz B, Ogbaa I, Frazier K, et al. Effects of LX4211, a dual sodium-dependent glucose cotransporters 1 and 2 inhibitor, on postprandial glucose, insulin, glucagon-like peptide 1, and peptide tyrosine tyrosine in a dose-timing study in healthy subjects. *Clin Ther* 2013;35:1162-1173.e8.
13. Dobbins RL, Greenway FL, Chen L, et al. Selective sodium-dependent glucose transporter 1 inhibitors block glucose absorption and impair glucose-dependent insulinotropic peptide release. *Am J Physiol Gastrointest Liver Physiol* 2015;308:G946-G954.
14. Sands AT, Zambrowicz BP, Rosenstock J, et al. Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes. *Diabetes Care* 2015;38:1181-8.
15. Zambrowicz B, Freiman J, Brown PM, et al. LX4211, a dual SGLT1/SGLT2 inhibitor, improved glycemic control in patients with type 2 diabetes in a randomized, placebo-controlled trial. *Clin Pharmacol Ther* 2012;92:158-69.
16. Bode BW, Garg SK. The emerging role of adjunctive noninsulin antihyperglycemic therapy in the management of type 1 diabetes. *Endocr Pract* 2016;22:220-30.
17. Einarson TR, Garg M, Kaur V, Hemels ME. Composite endpoints in trials of type-2 diabetes. *Diabetes Obes Metab* 2014;16:492-9.
18. Pieber TR, Famulla S, Eilbracht J, et al. Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo-controlled trial (EASE-1). *Diabetes Obes Metab* 2015;17:928-35.
19. Henry RR, Thakkar P, Tong C, Polidori D, Alba M. Efficacy and safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. *Diabetes Care* 2015;38:2258-65.
20. Mathieu C, Zinman B, Hemmingsson JU, et al. Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: the ADJUNCT ONE treat-to-target randomized trial. *Diabetes Care* 2016;39: 1702-10.
21. Petrie JR, Chaturvedi N, Ford I, et al. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2017;5:597-609.
22. Garg SK, Moser EG, Bode BW, et al. Effect of sitagliptin on post-prandial glucagon and GLP-1 levels in patients with type 1 diabetes: investigator-initiated, double-blind, randomized, placebo-controlled trial. *Endocr Pract* 2013;19:19-28.
23. Ellis SL, Moser EG, Snell-Bergeon JK, Rodionova AS, Hazenfield RM, Garg SK. Effect of sitagliptin on glucose control in adult patients with Type 1 diabetes: a pilot, double-blind, randomized, crossover trial. *Diabet Med* 2011;28:1176-81.
24. Lyons SK, Hermann JM, Miller KM, et al. Use of adjuvant pharmacotherapy in type 1 diabetes: international comparison of 49,367 individuals in the Diabetes Prospective Follow-up and T1D Exchange Registries. *Diabetes Care* 2017 August 2 (Epub ahead of print).
25. Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. *J Clin Endocrinol Metab* 2015;100:2849-52.
26. Handelsman Y, Henry RR, Bloomgarden ZT, et al. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the association of SGLT-2 inhibitors and diabetic ketoacidosis. *Endocr Pract* 2016;22:753-62.
27. Benstetter M. SGLT2 inhibitors: PRAC makes recommendations to minimise risk of diabetic ketoacidosis. Healthcare professionals should be aware of possible atypical cases. London: European Medicines Agency, 2016.
28. Hine J, Paterson H, Abrol E, Russell-Jones D, Herring R. SGLT inhibition and euglycaemic diabetic ketoacidosis. *Lancet Diabetes Endocrinol* 2015;3:503-4.
29. Erondur N, Desai M, Ways K, Meiningier G. Diabetic ketoacidosis and related events in the canagliflozin type 2 diabetes clinical program. *Diabetes Care* 2015;38: 1680-6.
30. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. *Diabetes Care* 2015;38:1687-93.
31. Hayami T, Kato Y, Kamiya H, et al. Case of ketoacidosis by a sodium-glucose cotransporter 2 inhibitor in a diabetic patient with a low-carbohydrate diet. *J Diabetes Investig* 2015;6:587-90.
32. Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. *J Diabetes Investig* 2016; 7:135-8.
33. Henry RR, Rosenstock J, Edelman S, et al. Exploring the potential of the SGLT2 inhibitor dapagliflozin in type 1 diabetes: a randomized, double-blind, placebo-controlled pilot study. *Diabetes Care* 2015;38: 412-9.
34. Fralick M, Schneeweiss S, Paterno E. Risk of diabetic ketoacidosis after initiation of an SGLT2 inhibitor. *N Engl J Med* 2017;376:2300-2.
35. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment. *Diabetes Care* 2017;40:Suppl 1: S64-S74.
36. Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R. Insulin pump therapy: a meta-analysis. *Diabetes Care* 2003;26:1079-87.
37. Heller S, White D, Lee E, et al. A cluster randomised trial, cost-effectiveness analysis and psychosocial evaluation of insulin pump therapy compared with multiple injections during flexible intensive insulin therapy for type 1 diabetes: the REPOSE Trial. *Health Technol Assess* 2017;21(20):1-278.
38. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. *Diabetes Technol Ther* 2017;19:155-63.
39. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. *JAMA* 2016;316:1407-8.

Copyright © 2017 Massachusetts Medical Society.